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Synthesis and evaluation of a novel series of quinoline derivatives with immunosuppressive activity

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ABSTRACT

A series of quinoline derivatives were synthesized and their immunosuppressive activity and cytotoxicity were evaluated with a T-cell functional assay and MTT method, respectively. Most of 5,7-dimethoxyquinolin-4-yl *ortho*-substituted benzoate derivatives (**18**, **22**, **24**, **28**, **31** and **37**) showed a quite stronger inhibitory activity compared to other analogs. Among the synthesized compounds, 5,7-dimethoxyquinolin-4-yl 2,6-dichlorobenzoate (**22**) and 5,7-dimethoxyquinolin-4-yl 4-methylbenzenesulfonate (**40**) exhibited a potent inhibitory activity without significant cytotoxicity at 10 μM concentration. The preliminary mechanism of the active compounds **22** and **40** was further clarified based on the fluorescence activated cell sorter (FACS) assay, and the compounds exerted immunosuppressive activity via inhibiting the T cell activation in a dose dependent manner.

1. Introduction

Immunosuppressant is an important class of clinical drugs used in prevention of the transplant rejection and treatment of autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and psoriasis. T-lymphocyte plays an integral role in transplant rejection and autoimmune diseases. Inhibition of T-lymphocyte activation has made cyclosporine A (CsA), tacrolimus (FK506), and sirolimus (rapamycin) become therapeutic immunosuppressants.[1] CsA and FK506 both interfere with a Ca^{2+}-sensitive T-cell signal transduction pathway, thereby preventing the activation of specific transcription factors involved in lymphokine gene expression.[2–4] Rapamycin suppresses T-cell activation mainly through inhibition of proliferation induced by growth-promoting lymphokines.[1] Although immunosuppressive drugs have been successfully used for organ transplantation and treatment of autoimmune diseases in clinic, their side effects including liver toxicity, nephrotoxicity, malignancy, infection, cardiovascular toxicity and others can not be neglected.[5–11] Many compounds derived from traditional Chinese medicines, such as artemisinin,[12,13] bakuchiol[14] and their analogs exhibit immunosuppressive activity by inhibiting T-cell activation and proliferation. The effort of searching for novel classes of potential immunosuppressive compounds with high efficacy and low toxicity has never stopped.

We have previously reported that a natural product, eucryphin with chromone skeleton possesses an immunological hepatocyte protective activity.[15] Quinoline skeleton, found in many synthetic and natural products, is a class of heterocyclic compounds which possess a variety of biological activities, such as antimalarial,[16] antiinflammatory,[17,18] antibacterial,[19] antiviral,[20] antitubercular,[21] and antitumor.[22] However, the effect of quinoline and its derivatives on immunosuppressive activity have not been studied sufficiently. Considering about the structural similarity of quinoline and chromone, we put our interest on quinoline derivatives in order to explore new chemical pharmacophores which might exhibit the immunosuppressive activity.

It has been reported that conjugates of fatty acids and pharmacophores could provide effective bioactivity, and different chain length greatly impacted the activity.[23] Therefore fatty acids might be effective moieties to improve the potency of the immunosuppressive activity. The same bioactivity improvements could also be observed on the glycosides and benzoic acid derivatives of natural products.[24–26] In the present study, a series of quinoline derivatives including fatty acid esters, glycosides and different substituted benzoic acid esters were synthesized. The immunosuppressive activity of the synthesized compounds was evaluated with T-cell functional assay and their cytotoxicity was tested using MTT method. The preliminary mechanism of some active compounds was further examined in a fluorescence activated cell sorter (FACS) assay.

2. Results and discussion

2.1. Chemistry

The syntheses of target compounds **4**–**9** are outlined in Scheme 1. Protection of the starting material 3,5-dimethoxyaniline (**1**) with

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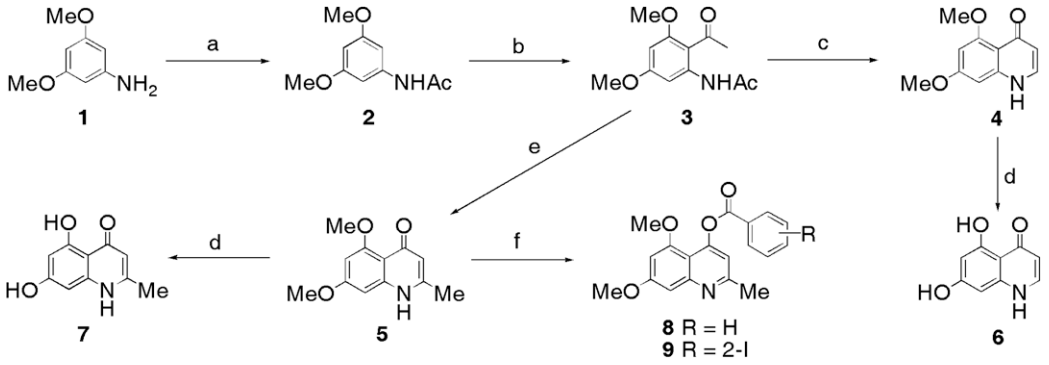


Scheme 1. Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, 0 °C, 1 h, 90%; (b) AcCl, $SnCl_4$, $ClCH_2CH_2Cl$, 0 °C, 4 h, 60%; (c) (i) HCOOEt, NaH, rt, 20 min; (ii) concd HCl, 0 °C, 3 h, 92%; (d) BBr_3, CH_2Cl_2, −78 °C to rt, 12 h, 45–50%; (e) ^{t}BuOK, ^{t}BuOH, reflux, 2 h, 95%; (f) R-PhCOCl, Et_3N, CH_2Cl_2, rt, 81–84%.

acetic anhydride afforded **2** in a satisfactory yield (90%). Compound **3** was prepared via a Friedel–Crafts reaction of compound **2** with acetyl chloride in the presence of anhydrous stannic chloride.[27] Compound **3** was then reacted with sodium hydride in ethyl formate at rt for 20 min, subsequently acidified using concentrated hydrochloric acid to provide **4** in 92% yield. This reaction might involve two steps, the hydrolysis of acetamide and intermolecular cyclization of *o*-aminoacetophenone.[28] An intramolecular cyclization of compound **3** in tertiary butyl alcohol in the presence of potassium *t*-butoxide afforded target compound **5** in 95% yield.[29] Demethylations of **4** and **5** using BBr_3 at −78 °C to rt afforded **6** and **7** in moderate yields. Compound **5** was then reacted with corresponding acyl chlorides to get **8** and **9**, respectively.

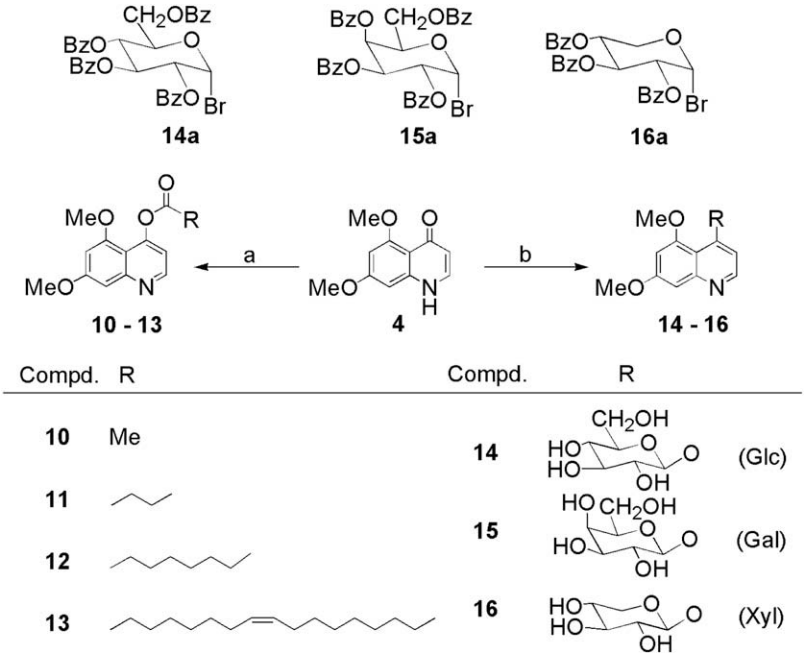
In order to understand the influences on activity, modifications at 4-OH of quinolines were conducted and compounds **10–40** were prepared. The synthesis routes are depicted in Schemes 2 and 3.

DDC/DMAP-mediated esterification was commonly used in organic synthesis for years.[30,31] As shown in Scheme 2, the reactions of **4** with different chain length of fatty acids using DCC as a condensing agent and DMAP as a catalyst provided corresponding fatty acid esters of **10**–**13**.

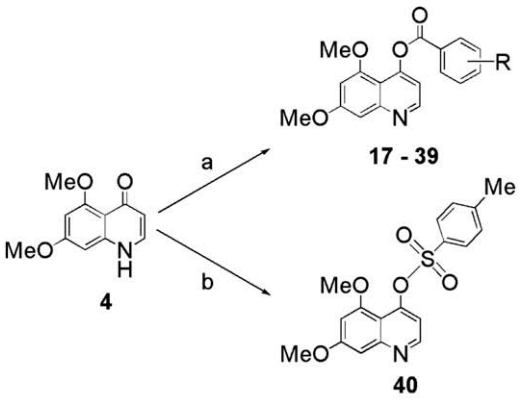
D-Sugar bromides **14a**–**16a** were prepared through benzoylation (BzCl in pyridine) and bromination (HBr in HOAc).[32,33] A phase-transfer-catalyzed method was applied for glycosidation due to its mild conditions and high yields.[34,35] The present glycosidations of **4** were performed by the reaction of acceptor **4** with donors (**14a**–**16a**) under the phase-transfer-catalyzed conditions (NaOH, Bu_4NBr, CH_2Cl_2–H_2O, reflux). Subsequent removal of the protecting groups (benzoyl) using sodium methoxide (cat.) in a mixed solution of MeOH and CH_2Cl_2 gave the target glycosides **14**–**16**.[36]

For the stereochemistry of the glycosidic bonds, bromides **14a**–**16a** were α-configuration which were identical with the reported data.[32,37] To target glycosides, all of the glycosidic bonds were β-configuration (**14**–**16**: H-1′, 5.80–5.89 ppm, d, J = 6.0–7.5 Hz).

Esterifications of **4** with 23 different substituted benzoic acids using EDCI and DMAP were outlined in Scheme 3. In the reactions, two condensing agents EDCI and DCC were tested. Although the



Scheme 2. Reagents and conditions: (a) RCOOH, DCC, DMAP, CH_2Cl_2, rt, 3 h, 70–75%; (b) (i) sugar donor, NaOH, TBAB, CH_2Cl_2/H_2O, reflux, 18 h; (ii) MeONa, CH_2Cl_2/MeOH, rt, 3 h, two steps 31–38%.



Compd.	R	Compd.	R
17	H	**29**	3-iodo
18	2-chloro	**30**	4-iodo
19	3-chloro	**31**	2-nitro
20	4-chloro	**32**	3-nitro
21	2,4-dichloro	**33**	4-nitro
22	2,6-dichloro	**34**	3,5-dinitro
23	3,5-dichloro	**35**	4-COOMe
24	2-bromo	**36**	2-fluoro
25	3-bromo	**37**	2-methyl
26	4-bromo	**38**	2-methoxy
27	3,5-dibromo	**39**	4-methoxy
28	2-iodo		

Scheme 3. Reagents and conditions: (a) R-PhCOOH, EDCI, DMAP, CH_2Cl_2, rt, 3–10 h, 60–90%; (b) *p*-TsCl, Et_3N, CH_2Cl_2, reflux, 8 h, 83%.

yield rates of two agents were the almost same, removal of condensing byproduct of DCC (DCHU) was quite difficult, while the EDCI's byproduct could be easily scoured off by diluted hydrochloric acid. Therefore, EDCI was used in the reaction. As expected, after removal of EDCI's byproduct and DMAP with diluted hydrochloric acid, only a simple crystallization process of the reaction product in methanol provided each pure target compound (**17**–**39**) without any chromatography purifications. Compound **40** was obtained in good yield by refluxing **4** with excess *p*-toluene sulfonyl chloride in the presence of triethyl amine.

2.2. Biological activity

The inhibitory activity on ConA-induced T cell proliferation of all the synthesized compounds was tested and their cytotoxicity on murine spleen cells was evaluated with MTT assay. The results of these compounds are summarized in Table 1.

As can been seen from Table 1, compounds **6** and **7** showed a weak inhibitory activity on ConA-induced T cell proliferation only at 100 μM. However, the compound **5,** a methylated derivative of **7** exhibited a moderate activity at the concentration of 100 and 30 μM. This result revealed that the methylation of hydroxyl groups might elevate the activity. While, the activity between compound **6** and its methylated product (**4**) showed no difference. Further modification of **5** with substituted benzoic acids (compounds **8** and **9**) did not exhibit any advancement of the activity compared with the same modifiers of **4** (compounds **17** and **28)** at lower concentration, which will discuss late.

As described above, fatty acid modification and glycosylation might improve the activity. Unfortunately, in the present studies, the fatty acids derivatives (**10–13**) and the glycosides (**14–16**) of **4** did not display ideal improvements of the inhibitory activity, although those compounds showed almost no cytotoxicity. To enhance the inhibitory activity of quinoline derivatives, different substituted benzoic acids were further introduced to the 4-hydroxy of quinolines, which resulted in compounds **17–39**. Fortunately, the most of 5,7-dimethoxyquinolin-4-yl substituted benzoate derivatives showed much stronger inhibitory activity than fatty acid derivatives and glycosides. As shown in Table 1, compounds **9** and **28** were obtained by modifying compounds **5** and **4** with *ortho*-iodobenzoic acid, the later showed much more potent inhibitory activity than **9**, which seemed that the activity of skeleton **4** derivatives is better than that of **5**. The interesting thing is the locations of substituent at benzoic acid were closely related to the immunosuppressive activity. The *ortho* located substituent derivatives (**18**, **22**, **24, 28**, **31**, and **37**) had more potent activity than other derivatives. Furthermore, the inhibitory activity of compounds modified with *ortho*-halogen-substituted benzoic acids was increased in the following order: F < Cl < Br < I. Fortunately, compound **40** displayed very good inhibitory activity and without cytotoxicity at three concentrations (10, 30 and 100 μM), which indicated that the *para*-toluene sulfonyl may be a potentially active functional group of immunosuppressor.

For proving these results obtained by MTT assay, several active compounds (**18**, **22**, **24**, **28**, **31**, **37** and **40**) were assessed their effect on T cell proliferation induced by ConA in terms of uptake of [^{3}H]thymidine which is more sensitive and accurate than MTT assay. As shown in Table 2, the results were similar and consistent with the data got from MTT assay as described above. It is noteworthy to indicate that compound **22** got an inhibition rate of 35% at 1 μM.

To further understand the immunosuppressive mechanism of these derivatives, the fluorescence activated cell sorter (FACS) assay was applied to assess the effect of some active compounds (**18**, **22**, **24**, **28**, **31**, **37** and **40**) on T cell activation induced by ConA. As shown in Table 3, compared to control, the percentage of activated T cells was increased from 38.39 to 93.84 when stimulated with ConA. CsA, a clinically available immunosuppressor, inhibited the activation to control level. Both **22** and **40** inhibited the T cell activation in a dose dependent manner. The other quinoline derivatives (**18**, **24**, **28**, **31** and **37**) showed weak effects which indicated that they did not suppress T cell proliferation through inhibiting cell activation.

3. Conclusion

We have synthesized a series of quinoline derivatives with inhibitory effect on ConA-induced T cell proliferation. Quinoline with methylated-hydroxyl groups displayed a better immunosuppressive activity than unmethylated one. Fatty acid derivatives and glycosides of 5,7-dimethoxyquinolin-4-yl did not show any benefit on the improvement of the activity, while, benzoic acid derivatives positively impacted the activity. *ortho*-Substituted benzoate derivatives exhibited a close correlation with the stronger activity and no significant cytotoxicity at 10 μM was observed. Especially, compound **22** and **40** exerted a strongest immunosuppressive activity by inhibiting the T cell activation in a dose dependent manner. The present results revealed that the quinoline derivatives as a new class of immunosuppressive leads deserve further studies. The in vivo activity and further detailed immunosuppressive mechanism of **22** and **40** are in process in our lab.

Table 1
Effect of quinoline derivatives **4**–**40** on murine T lymphocyte proliferation induced by ConA (5 μg/mL) measured with MTT method

Compound	Inhibition rate (%)			Cytotoxicity (growth inhibition in %)		
	10 (μM)	30 (μM)	100 (μM)	10 (μM)	30 (μM)	100 (μM)
4	0.1 ± 2.6	3.7 ± 2.9	12.3 ± 6.9	6.1 ± 5.8	7.8 ± 3.6	7.5 ± 4.1
5	15.9 ± 2.8*	35.4 ± 2.4**	57.2 ± 2.2**	6.5 ± 0.7	14.7 ± 8.5	23.6 ± 4.7*
6	−0.9 ± 1.5	1.7 ± 1.9	18.0 ± 6.4*	1.8 ± 9.2	10.9 ± 7.4	8.6 ± 6.6
7	7.5 ± 4.9	4.4 ± 3.0	26.7 ± 2.9**	9.1 ± 7.8	9.9 ± 1.5	11.2 ± 13.4
8	5.7 ± 4.4	34.8 ± 14.9	81.5 ± 8.0**	−7.6 ± 4.9	−0.2 ± 7.1	13.7 ± 8.7
9	19.9 ± 3.0**	54.0 ± 6.9**	91.5 ± 2.2**	−3.4 ± 5.1	18.2 ± 7.6	37.6 ± 3.5**
10	2.2 ± 2.3	9.7 ± 2.8*	22.7 ± 6.8*	8.3 ± 4.1	11.2 ± 5.9	11.3 ± 6.0
11	4.1 ± 3.7	5.3 ± 4.6	13.9 ± 2.3**	4.5 ± 3.7	10.5 ± 14.0	9.4 ± 9.0
12	4.4 ± 2.2	2.0 ± 6.1	31.9 ± 4.7**	6.4 ± 5.9	2.0 ± 6.9	11.6 ± 12.6
13	4.4 ± 3.3	8.5 ± 1.9*	22.2 ± 2.5**	4.1 ± 6.0	8.8 ± 8.8	7.2 ± 3.9
14	3.6 ± 2.4	6.0 ± 3.9	20.4 ± 3.0**	7.6 ± 7.1	9.1 ± 3.8	9.5 ± 4.3
15	4.2 ± 2.3	11.2 ± 3.9*	17.8 ± 3.3*	6.2 ± 4.8	4.2 ± 5.6	17.0 ± 9.3
16	10.3 ± 4.9	14.9 ± 5.7*	41.0 ± 1.2**	6.9 ± 6.5	9.1 ± 7.1	11.2 ± 3.3*
17	6.2 ± 1.1*	13.1 ± 1.4**	35.4 ± 1.0**	0.0 ± 5.1	4.6 ± 4.0	7.7 ± 6.9
18	46.1 ± 4.7**	73.7 ± 5.7**	89.8 ± 1.8**	2.9 ± 6.9	6.6 ± 5.4	39.8 ± 5.0**
19	20.6 ± 7.8*	42.0 ± 3.1**	90.8 ± 2.1**	3.1 ± 4.4	9.4 ± 8.4	12.2 ± 12.3
20	30.1 ± 3.9**	47.4 ± 11.4*	86.3 ± 2.8**	3.4 ± 1.9	0.3 ± 11.9	21.9 ± 5.5*
21	35.3 ± 5.2**	62.3 ± 10.6**	79.2 ± 5.6**	16.5 ± 9.0	20.8 ± 7.5	22.7 ± 5.6*
22	94.0 ± 0.2**	94.6 ± 0.2**	94.3 ± 0.5**	10.9 ± 6.3	52.7 ± 3.7**	83.4 ± 1.4**
23	3.9 ± 2.6	5.1 ± 2.6	7.9 ± 2.4*	3.4 ± 2.7	10.7 ± 8.4	7.2 ± 3.4
24	51.2 ± 16.0*	85.7 ± 4.1**	93.3 ± 4.1**	9.8 ± 5.2	22.5 ± 9.6	29.2 ± 6.4*
25	16.9 ± 5.7*	48.8 ± 13.4*	91.0 ± 3.1**	1.7 ± 11.6	1.7 ± 3.6	21.0 ± 7.1*
26	9.2 ± 0.6**	17.5 ± 0.4**	48.2 ± 11.2*	8.6 ± 9.4	7.3 ± 10.0	20.7 ± 7.9*
27	6.4 ± 4.1	10.0 ± 9.4	12.1 ± 1.8	5.5 ± 4.5	9.4 ± 7.7	6.3 ± 4.9
28	63.0 ± 10.9**	90.6 ± 2.6**	93.0 ± 4.4**	14.3 ± 10.9	26.5 ± 11.7	54.7 ± 12.4*
29	24.7 ± 5.7*	50.5 ± 11.3*	85.2 ± 2.9**	3.0 ± 10.0	5.6 ± 12.0	11.6 ± 16.7
30	26.4 ± 7.8*	47.2 ± 5.8**	91.3 ± 4.5**	6.0 ± 6.0	6.6 ± 5.3	23.4 ± 10.8
31	38.6 ± 12.6*	75.2 ± 3.8**	90.5 ± 3.7**	10.7 ± 3.9	32.0 ± 5.2**	33.4 ± 0.2**
32	18.8 ± 6.1*	42.0 ± 3.6**	82.8 ± 5.7**	3.3 ± 5.1	8.1 ± 10.0	12.2 ± 11.8
33	18.4 ± 0.4**	34.1 ± 2.0**	64.0 ± 9.9**	6.0 ± 14.0	11.1 ± 16.9	9.5 ± 15.7
34	6.3 ± 4.6	5.1 ± 4.3	5.6 ± 5.0	3.4 ± 7.0	9.5 ± 7.8	13.4 ± 7.4
35	15.7 ± 9.9	27.8 ± 8.7*	91.4 ± 2.5**	6.6 ± 5.3	2.2 ± 18.5	23.6 ± 20.8
36	9.3 ± 6.7	14.3 ± 4.4*	31.0 ± 5.8*	7.7 ± 15.3	12.8 ± 16.3	19.5 ± 18.1
37	70.3 ± 4.6**	91.4 ± 0.7**	92.2 ± 2.5**	9.4 ± 12.2	53.9 ± 7.6**	64.0 ± 5.7**
38	11.3 ± 2.9*	35.2 ± 17.5	85.3 ± 8.2**	10.3 ± 3.5	17.6 ± 7.2	47.9 ± 13.5*
39	7.8 ± 3.8	11.0 ± 4.7	17.7 ± 3.2*	8.2 ± 7.5	11.3 ± 5.6	13.4 ± 10.2
40	82.3 ± 5.9**	94.7 ± 0.2**	94.2 ± 0.3**	6.2 ± 17.2	5.4 ± 15.2	13.2 ± 16.8
CsA (1 μM)		86.4 ± 5.4**			8.70 ± 12.4	

Data are expressed as mean ± S.D., $n = 3$. Significant differences compared with control group (0.0%).
* $p < 0.05$.
** $p < 0.01$.

4. Experimental

4.1. Synthesis

4.1.1. General

All reagents and solvents were commercially available and used without further purification. Melting points were determined on a Taike X-4 digital micromelting point apparatus and uncorrected. ^1H and ^{13}C NMR spectra were taken on a Bruker DPX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). ESI-HR-MS were obtained on Esquire 4000 mass spectrometer. TLC was carried out on precoated Kieselgel F254 plates (0.25 mm), and spots were detected under a UV lamp (254 nm).

4.1.2. *N*-(3,5-Dimethoxyphenyl)acetamide (2)

To a solution of **1** (15.3 g, 0.10 mol) in CH_2Cl_2 (250 mL) at 0 °C was added triethylamine (16.8 mL, 0.12 mol) and then acetic

Table 2
Effect of some selected quinoline derivatives on murine T lymphocyte proliferation induced by ConA (5 μg/mL) measured in terms of uptake of [^{3}H] thymidine

Compound	Inhibition rate (%)		
	1 (μM)	10 (μM)	30 (μM)
18	4.3 ± 4.1	37.9 ± 1.4**	52.0 ± 0.8**
22	34.7 ± 2.6**	97.8 ± 0.6**	99.2 ± 0.2**
24	4.8 ± 7.8	42.0 ± 1.7**	85.4 ± 1.8**
28	8.2 ± 6.0	47.5 ± 1.1**	87.1 ± 1.2**
31	10.2 ± 5.6	21.1 ± 1.2**	64.6 ± 1.1**
37	2.2 ± 3.0	55.4 ± 1.3**	94.6 ± 0.1**
40	12.9 ± 2.8	87.7 ± 1.0**	98.9 ± 0.5**
CsA (1 μM)		95.0 ± 0.4**	

Data are expressed as mean ± S.D., $n = 3$. Significant differences compared with control group (0.0%).
** $p < 0.01$.

Table 3
Effect of some selected quinoline derivatives on murine T cell activation induced by ConA (5 μg/mL) measured with FACS assay

Compound	Activated T cell% (CD4+CD25+/CD4+)			
	1 (μM)	3 (μM)	10 (μM)	30 (μM)
18	95.63	92.80	93.10	90.86
22	92.96	88.80	59.64	19.41
24	94.92	93.23	93.63	86.21
28	93.10	91.87	90.04	83.23
31	94.79	94.01	92.75	86.19
37	93.81	92.54	85.45	75.65
40	85.74	81.66	68.39	13.70
Alone		38.39		
ConA		93.84		
CsA (1 μM)		35.14		

anhydride (11.4 mL, 0.12 mol) was added dropwise. The reaction mixture was stirred for 1 h, quenched by the addition of water (30 mL), and then the pH was adjusted to 7 by adding saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The combined organic layer was washed with diluted HCl, saturated $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give **2**. Yield: 90%; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.15 (3H, s), 3.76 (6H, s), 6.22 (1H, s), 6.74 (2H, s), 7.34 (1H, br).

4.1.3. *N*-(2-Acetyl-3,5-dimethoxyphenyl)acetamide (3)

To a solution of **2** (12.4 g 63.5 mmol) in anhydrous $ClCH_2CH_2Cl$ (250 mL) at 0 °C was added anhydrous $SnCl_4$ (15 mL 128.4 mmol) dropwise and acetyl chloride (10 mL 140.1 mmol) was added dropwise. The solution was stirred at rt for 4 h and poured into 100 mL ice water. The aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, chromatography of the crude product on silica gel, eluting with PE/EtOAc (4/1) afforded **3**. Yield: 60%; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.17 (3H, s), 2.56 (3H, s), 3.85 (6H, s), 6.17 (1H, s), 7.95 (1H, s), 11.73 (1H, br).

4.1.4. 5,7-Dimethoxyquinolin-4(1*H*)-one (4)

To a solution of **3** (3.0 g, 12.6 mmol) in ethyl formate (40 mL) was added NaH (3.1 g, 60% in mineral oil, 77 mmol). After a short induction period, an exothermal reaction was carried out and the suspension began to reflux. The reaction solution was stirred at rt for 20 min, then cooled to 0 °C. The reaction was quenched by the addition of water (1 mL), subsequently concentrated HCl (9 mL) was added, and the suspension was stirred at 0 °C for 4 h. After adjusting the pH to 7 by 5 M NaOH solution, the resulting solid was filtered, washed with water, dioxane, ethyl acetate, and then dried to give **4**. Yield: 92%; mp 233–235 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ: 3.72 (3H, s), 3.78 (3H, s), 5.74 (1H, d, J = 7.0 Hz), 6.26 (1H, s), 6.42 (1H, s), 7.55 (1H, d, J = 7.0 Hz), 11.22 (1H, br); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.68, 56.05, 91.87, 94.79, 111.44, 111.87, 137.38, 144.68, 161.35, 162.21, 176.75; HRMS-ESI (m/z): calcd for $C_{11}H_{12}NO_3$ $[M+H]^+$: 206.0817, found: 206.0810.

4.1.5. 5,7-Dimethoxy-2-methylquinolin-4(1*H*)-one (5)

To a solution of **3** (1.0 g, 4.2 mmol) in ^{t}BuOH (30 mL) was added ^{t}BuOK (2.3 g, 21 mmol), and the suspension was refluxed for 2 h. The pH of the suspension was adjusted to 7 by adding diluted hydrochloric acid. The resulting solid was filtered, washed with water and dried to provide **5**. Yield: 95%; mp 263–265 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.49 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 6.02 (1H, s), 6.30 (1H, s), 6.44 (1H, s), 11.38 (1H, br); ^{13}C NMR (CF_3COOD, 75 MHz) δ: 24.24, 54.83, 55.08, 107.74, 108.71, 112.46, 119.97, 159.00, 160.73, 161.30, 161.88, 162.45; HRMS-ESI (m/z): calcd for $C_{12}H_{14}NO_3$ $[M+H]^+$: 220.0974, found: 220.0969.

4.1.6. General procedure for compounds 6 and 7

To a solution of **4** or **5** (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added BBr_3 solution (2.2 mL, 1 M in CH_2Cl_2, 2.2 mmol) dropwise at −78 °C, and the mixture was stirred at rt for 24 h. Water (1 mL) was added to quench the reaction, and the solvent was evaporated in vacuo. Chromatography of the crude product on silica gel, eluting with CH_2Cl_2/MeOH afforded **6** or **7**.

4.1.6.1. 5,7-Dihydroxyquinolin-4(1*H*)-one (6). Yield: 45%; Carbonization before mp; ^1H NMR (CD_3OD, 300 MHz) δ: 6.03 (1H, d, J = 7.2 Hz), 6.11 (1H, d, J = 1.6 Hz), 6.25 (1H, d, J = 1.6 Hz), 7.70 (1H, d, J = 7.2 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ: 91.51, 97.73, 106.11, 107.91, 139.63, 142.55, 162.32, 162.82, 181.90; HRMS-ESI (m/z): calcd for $C_9H_8NO_3$ $[M+H]^+$: 178.0504, found: 178.0498.

4.1.6.2. 5,7-Dihydroxy-2-methylquinolin-4(1*H*)-one (7). Yield: 50%; Carbonization before mp; ^1H NMR (CF_3COOD, 300 MHz) δ: 3.07 (3H, s), 6.82 (1H, s), 6.86 (2H, s); ^{13}C NMR (CF_3COOD, 75 MHz) δ: 23.96, 107.48, 108.66, 112.41, 119.91, 159.45, 160.94, 161.52, 162.10, 162.68; HRMS-ESI (m/z): calcd for $C_{16}H_{10}NO_3$ $[M+H]^+$: 192.0661, found: 192.0654.

4.1.7. General procedure for compounds 8 and 9

To a solution of **5** (219 mg, 1 mmol) in CH_2Cl_2 (10 mL) at rt was added Et_3N (0.28 mL, 2 mmol) and corresponding substituted benzoyl chloride (1.2 mmol). The reaction solution was stirred for 3 h, quenched by the addition of water (10 mL), and then the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with diluted hydrochloric acid, saturated $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was recrystallized in MeOH to yield **8** and **9**.

4.1.7.1. 5,7-Dimethoxy-2-methylquinolin-4-yl benzoate (8). Yield: 84%; mp 183–185 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.85 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 6.50 (1H, d, J = 2.2 Hz), 6.87 (1H, s), 6.98 (1H, d, J = 2.2 Hz), 7.51 (2H, t, J = 7.5 Hz), 7.64 (1H, t, J = 7.5 Hz), 8.25 (2H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.67, 55.68, 55.71, 98.71, 100.54, 114.48, 115.68, 128.68, 129.38, 130.57, 133.94, 150.62, 150.72, 157.29, 158.83, 161.27, 165.10; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1236, found: 324.1233.

4.1.7.2. 5,7-Dimethoxy-2-methylquinolin-4-yl 2-iodobenzoate (9). Yield: 81%; mp 145–146 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.86 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 6.50 (1H, d, J = 2.2 Hz), 6.91 (1H, s), 6.96 (1H, d, J = 2.2 Hz), 7.22 (1H, td, J = 7.8, 1.5 Hz), 7.48 (1H, t, J = 7.8 Hz), 8.08 (1H, d, J = 7.8 Hz), 8.20 (1H, dd, J = 7.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.71, 55.70, 55.73, 95.29, 98.78, 100.54, 114.28, 115.75, 128.19, 132.32, 133.19, 133.67, 142.04, 150.57, 150.85, 156.90, 158.81, 161.29, 164.30; HRMS-ESI (m/z): calcd for $C_{19}H_{17}INO_4$ $[M+H]^+$: 450.0202, found: 450.0205.

4.1.8. General procedure for compounds (10–13)

To a solution of **4** (205 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added corresponding fatty acid (1.2 mmol), DCC (247 mg, 1.2 mmol) and a few crystals of DMAP. The suspension was stirred for 3 h. The resulting solid was filtered and the filtrate was washed with diluted HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification through silica gel chromatography eluting with PE/EtOAc afforded corresponding compounds **10–13.**

4.1.8.1. 5,7-Dimethoxyquinolin-4-yl acetate (10). Yield 70%; mp 225–227 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 6.51 (1H, d, J = 2.1 Hz), 6.86 (1H, d, J = 4.8 Hz), 7.08 (1H, d, J = 2.1 Hz), 8.73 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.59, 55.62, 55.92, 92.30, 96.32, 109.92, 110.82, 139.46, 144.98, 160.24, 163.09, 176.01, 177.30; HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_4$ $[M+H]^+$: 248.0923, found: 248.0924.

4.1.8.2. 5,7-Dimethoxyquinolin-4-yl pentanoate (11). Yield 72%; mp 103–105 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (3H, t, J = 7.5 Hz), 1.47 (2H, sextet, J = 7.5 Hz), 1.77 (2H, quintet, J = 7.5 Hz), 2.64 (2H, t, J = 7.5 Hz), 3.86 (3H, s), 3.91 (3H, s), 6.51 (1H, d, J = 1.8 Hz), 6.84 (1H, d, J = 4.5 Hz), 7.06 (1H, d, J = 1.8 Hz), 8.72 (1H, d, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.83, 22.35, 27.15, 34.39, 55.51, 55.78, 92.09, 96.04, 110.23, 111.09, 139.05, 144.89, 160.39, 162.98, 177.94, 178.77; HRMS-ESI (m/z): calcd for $C_{16}H_{20}NO_4$ $[M+H]^+$: 290.1392, found: 290.1386.

4.1.8.3. 5,7-Dimethoxyquinolin-4-yl nonanoate (12). Yield 72%; mp 73–76 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (3H, t, J = 6.3 Hz), 1.26 (10H, m), 1.64 (2H, m), 2.35 (2H, t, J = 7.5 Hz), 3.73 (3H, s), 3.77 (3H, s), 6.26 (1H, s), 6.30 (1H, d, J = 6.9 Hz), 6.65 (1H, s), 7.72 (1H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.22, 22.76, 25.07, 29.26, 29.29, 29.38, 31.93, 34.60, 55.58, 55.90, 92.53, 96.12, 110.12, 110.97, 139.54, 145.23, 160.28, 162.88, 177.22, 179.15; HRMS-ESI (m/z): calcd for $C_{20}H_{28}NO_4$ $[M+H]^+$: 346.2018, found: 346.2006.

4.1.8.4. 5,7-Dimethoxyquinolin-4-yl oleate (13). Yield 75%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (3H, m), 1.25–1.34 (20H, m), 1.77 (2H, t, J = 7.2 Hz), 2.01 (4H, m), 2.63 (2H, t, J = 7.5 Hz), 3.86 (3H, s), 3.92 (3H, s), 5.34 (2H, s), 6.51 (1H, d, J = 1.8 Hz), 6.84 (1H, d, J = 4.8 Hz), 7.06 (1H, d, J = 1.8 Hz), 8.72 (1H, d, J = 4.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.20, 24.66, 24.57, 27.15, 27.21, 29.10, 29.22, 29.31, 29.50, 29.68, 29.74, 31.76, 34.16, 55.57, 56.11, 99.71, 100.56, 110.94, 112.64, 122.66, 122.96, 151.35, 153.18, 154.86, 155.83, 161.15, 171.66; HRMS-ESI (m/z): calcd for $C_{29}H_{44}NO_4$ $[M+H]^+$: 470.3270 found:470.3265.

4.1.9. General procedure for compounds (14–16)

To a solution of **4** (205 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) and water (20 mL) was added sugar donor (1.5 mmol), NaOH (320 mg, 8.0 mmol) and TBAB (386 mg, 1.2 mmol). The suspension was stirred at 50 °C for 18 h. Water (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with diluted acid, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification through silica gel chromatography eluting with PE/EtOAc afforded corresponding product. The product was dissolved in a mixed solution of CH_2Cl_2 (3 mL) and MeOH (3 mL), and MeONa (catalytic amount) was added. The mixture was stirred for 3 h. The reaction was quenched by the addition of water (2 mL), and the pH was adjusted to 7. The resulting solid was filtered, washed with a little water and dried to obtain **14–16**.

4.1.9.1. 5,7-Dimethoxyquinolin-4-yl β-D-glucopyranosyl ether (14). Yield 31%; mp 188–190 °C; ^{1}H NMR (C_5D_5N, 300 MHz) δ: 3.63 (3H, s), 3.76 (3H, s), 4.21 (1H, s), 4.40–4.58 (5H, m), 5.86 (1H, d, J = 6.8 Hz), 6.65 (1H, s), 7.30 (1H, d, J = 4.8 Hz), 7.35 (1H, s), 8.86 (1H, d, J = 4.8 Hz); ^{13}C NMR (C_5D_5N, 75 MHz) δ: 56.92, 57.70, 63.75, 72.52, 76.53, 80.20, 80.74, 100.89, 102.71, 102.84, 105.20, 111.03, 153.67, 155.71, 160.08, 162.81, 164.12; HRMS-ESI (m/z): calcd for $C_{17}H_{22}NO_8$ $[M+H]^+$: 368.1345, found: 368.1344.

4.1.9.2. 5,7-Dimethoxyquinolin-4-yl β-D-galactopyranosyl ether (15). Yield 33%; mp 214–216 °C; ^{1}H NMR (C_5D_5N, 300 MHz) δ: 3.55 (3H, s), 3.78 (3H, s), 4.36–4.55 (4H, m), 4.68 (1H, d, J = 3.0 Hz), 4.96 (1H, dd, J = 9.3, 7.8 Hz), 5.80 (1H, d, J = 7.5 Hz), 6.64 (1H, d, J = 2.4 Hz), 7.35 (1H, d, J = 5.4 Hz), 7.36 (1H, d, J = 2.4 Hz), 8.86 (1H, d, J = 5.4 Hz). ^{13}C NMR (C_5D_5N, 75 MHz) δ: 56.46, 57.29, 63.66, 71.22, 73.50, 76.55, 79.17, 100.54, 102.42, 103.40, 104.91, 109.08, 153.38, 155.27, 159.82, 162.48, 163.97; HRMS-ESI (m/z): calcd for $C_{17}H_{22}NO_8$ $[M+H]^+$: 368.1345, found: 368.1345.

4.1.9.3. 5,7-Dimethoxyquinolin-4-yl β-D-xylopyranosyl ether (16). Yield 38%; mp 118–120 °C; ^{1}H NMR (C_5D_5N, 300 MHz) δ: 3.72 (3H, s), 3.78 (3H, s), 3.99 (1H, dd, J = 11.2, 7.8 Hz), 4.31–4.50 (4H, m), 5.89 (1H, d, J = 6.0 Hz), 6.67 (1H, d, J = 2.1 Hz), 7.26 (1H, d, J = 5.4 Hz), 7.39 (1H, d, J = 2.1 Hz), 8.87 (1H, d, J = 5.4 Hz); ^{13}C NMR (C_5D_5N, 75 MHz) δ: 56.91, 57.64, 67.96, 72.04, 75.21, 78.27, 100.91, 102.65, 102.91, 105.14, 110.91, 153.55, 155.60, 159.72, 162.83, 163.58; HRMS-ESI (m/z): calcd for $C_{16}H_{20}NO_7$ $[M+H]^+$: 338.1240, found: 338.1242.

4.1.10. General procedure for compounds (17–39)

To a solution of **4** (205 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) at rt was added substituted benzoic acid (1.2 mmol), EDCI (288 mg, 1.5 mmol) and a few crystals of DMAP. The solution was stirred for 6 h. Water (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with diluted hydrochloric acid, saturated $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was recrystallized in MeOH to yield **17–39**.

4.1.10.1. 5,7-Dimethoxyquinolin-4-yl benzoate (17). Yield 78%; mp 169–171 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.55 (3H, s), 3.93 (3H, s), 6.47 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.8 Hz), 7.10 (1H, d, J = 2.1 Hz), 7.54 (2H, t, J = 7.5 Hz), 7.67 (1H, t, 7.5 Hz), 8.23 (2H, d, J = 7.5 Hz), 8.79 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.58, 55.81, 99.59, 100.51, 110.81, 112.80, 128.58, 129.86, 130.29, 133.55, 151.45, 153.24, 155.19, 155.89, 161.25, 164.95; HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO_4$ $[M+H]^+$: 310.1079, found: 310.1072.

4.1.10.2. 5,7-Dimethoxyquinolin-4-yl 2-chlorobenzoate (18). Yield: 80%; mp 155–157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.71 (3H, s), 3.96 (3H, s), 6.53 (1H, d, J = 1.8 Hz), 7.04 (1H, d, J = 4.8 Hz), 7.12 (1H, d, J = 1.8 Hz), 7.47 (1H, m), 7.56 (2H, m), 8.26 (1H, d, J = 7.2 Hz), 8.82 (1H, d, J = 4.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.61, 55.94, 99.71, 100.65, 110.74, 112.71, 126.71, 128.41, 131.57, 132.56, 133.43, 135.10, 151.52, 153.29, 154.63, 155.76, 161.27, 162.91; HRMS-ESI (m/z): calcd for $C_{18}H_{15}ClNO_4$ $[M+H]^+$: 344.0690, found: 344.0682.

4.1.10.3. 5,7-Dimethoxyquinolin-4-yl 3-chlorobenzoate (19). Yield: 85%; mp 149–151 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.57 (3H, s), 3.92 (3H, s), 6.48 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.8 Hz), 7.11 (1H, d, J = 2.1 Hz), 7.48 (1H, t, J = 8.0 Hz), 7.64 (1H, d, J = 8.0 Hz), 8.11 (1H, d, J = 8.0 Hz), 8.22 (1H, s), 8.79 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.77, 56.05, 99.88, 100.72, 110.68, 112.76, 128.55, 130.10, 130.44, 131.40, 133.77, 134.92, 151.60, 153.38, 154.96, 155.87, 161.46, 163.88; HRMS-ESI (m/z): calcd for $C_{18}H_{14}ClNO_4Na$ $[M+Na]^+$: 366.0509, found: 366.0505.

4.1.10.4. 5,7-Dimethoxyquinolin-4-yl 4-chlorobenzoate (20). Yield: 87%; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.56 (3H, s), 3.93 (3H, s), 6.49 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.9 Hz), 7.11 (1H, d, J = 2.1 Hz), 7.53 (2H, d, J = 8.5 Hz), 8.17 (2H, d, J = 8.5 Hz), 8.79 (1H, d, J = 4.9 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.77, 56.01, 99.85, 100.67, 110.78, 112.83, 128.09, 129.14, 131.82, 140.27, 151.54, 153.32, 155.10, 155.89, 161.46, 164.21; HRMS-ESI (m/z): calcd for $C_{18}H_{14}ClNO_4Na$ $[M+Na]^+$: 366.0509, found: 366.0508.

4.1.10.5. 5,7-Dimethoxyquinolin-4-yl 2,4-dichlorobenzoate (21). Yield: 81%; mp 174–175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.67 (3H, s), 3.92 (3H, s), 6.51 (1H, d, J = 2.1 Hz), 6.99 (1H, d, J = 4.8 Hz), 7.10 (1H, d, J = 2.1 Hz), 7.42 (1H, dd, J = 8.5, 1.8 Hz), 7.58 (1H, d, J = 1.8 Hz), 8.19 (1H, d, J = 8.5 Hz), 8.79 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.78, 56.12, 99.94, 100.83, 110.69, 112.77, 126.83, 127.34, 131.64, 133.73, 136.42, 139.50, 151.65, 153.40, 154.55, 155.75, 161.43, 162.22; HRMS-ESI (m/z): calcd for $C_{18}H_{14}Cl_2NO_4$ $[M+H]^+$: 378.0300, found: 378.0296.

4.1.10.6. 5,7-Dimethoxyquinolin-4-yl 2,6-dichlorobenzoate (22). Yield: 60%; mp 173–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (3H, s), 3.92 (3H, s), 6.53 (1H, d, J = 2.1 Hz), 7.08 (1H, d, J = 2.1 Hz), 7.21 (1H, d, J = 5.0 Hz), 7.32–7.43 (3H, m), 8.80 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.74, 56.15, 99.80, 100.39, 110.70, 112.53, 128.62, 131.84, 131.94, 132.97, 151.31, 153.66, 154.54, 156.45, 161.56, 162.45; HRMS-ESI (m/z): calcd for $C_{18}H_{14}Cl_2NO_4$ $[M+H]^+$: 378.0300, found: 378.0305.

4.1.10.7. 5,7-Dimethoxyquinolin-4-yl 3,5-dichlorobenzoate (23). Yield: 88%; mp 232–233 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.61 (3H, s), 3.94 (3H, s), 6.51 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.9 Hz), 7.12 (1H, d, J = 2.1 Hz), 7.66 (1H, t, J = 1.8 Hz), 8.11 (2H, d, J = 1.8 Hz), 8.80 (1H, d, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.83, 56.18, 100.06, 100.78, 110.47, 112.61, 128.78, 132.50, 133.61, 135.75, 151.58, 153.38, 154.68, 155.76, 161.55, 162.77; HRMS-ESI (m/z): calcd for $C_{18}H_{14}Cl_2NO_4$ $[M+H]^+$: 378.0300, found: 378.0303.

4.1.10.8. 5,7-Dimethoxyquinolin-4-yl 2-bromobenzoate (24). Yield: 90%; mp 155–156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.70 (3H, s), 3.93 (3H, s), 6.52 (1H, d, J = 1.9 Hz), 7.02 (1H, d, J = 5.0 Hz), 7.11 (1H, d, J = 1.9 Hz), 7.42–7.52 (2H, m), 7.78 (1H, d, J = 7.8 Hz), 8.23 (1H, dd, J = 7.4, 1.8 Hz), 8.79 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.77, 56.15, 99.88, 100.71, 110.86, 112.83, 123.28, 127.44, 130.29, 132.77, 133.62, 135.12, 151.58, 153.34, 154.83, 155.88, 161.44, 163.47; HRMS-ESI (m/z): calcd for $C_{18}H_{15}BrNO_4$ $[M+H]^+$: 388.0184, found: 388.0187.

4.1.10.9. 5,7-Dimethoxyquinolin-4-yl 3-bromobenzoate (25). Yield: 88%; mp 165–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.58 (3H, s), 3.93 (3H, s), 6.49 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.8 Hz), 7.11 (1H, d, J = 2.1 Hz), 7.43 (1H, t, J = 8.0 Hz), 7.79 (1H, d, J = 8.0 Hz), 8.16 (1H, d, J = 8.0 Hz), 8.39 (1H, s), 8.79 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.76, 56.05, 99.87, 100.71, 110.69, 112.73, 122.78, 128.98, 130.32, 131.57, 133.35, 136.66, 151.57, 153.36, 154.94, 155.86, 161.44, 163.72; HRMS-ESI (m/z): calcd for $C_{18}H_{15}BrNO_4$ $[M+H]^+$: 388.0184, found: 388.0179.

4.1.10.10. 5,7-Dimethoxyquinolin-4-yl 4-bromobenzoate (26). Yield: 86%; mp 165–166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.54 (3H, s), 3.91 (3H, s), 6.47 (1H, d, J = 2.2 Hz), 6.98 (1H, d, J = 4.9 Hz), 7.09 (1H, d, J = 2.2 Hz), 7.67 (2H, d, J = 8.5 Hz), 8.08 (2H, d, J = 8.5 Hz), 8.78 (1H, d, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.72, 55.98, 99.79, 100.68, 110.70, 112.79, 128.53, 128.94, 131.59, 131.89, 132.10, 151.58, 153.35, 154.99, 155.83, 161.39, 164.33; HRMS-ESI (m/z): calcd for $C_{18}H_{15}BrNO_4$ $[M+H]^+$: 388.0184, found: 388.0187.

4.1.10.11. 5,7-Dimethoxyquinolin-4-yl 3,5-dibromobenzoate (27). Yield: 86%; mp 224–225 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.62 (3H, s), 3.94 (3H, s), 6.51 (1H, d, J = 2.0 Hz), 7.00 (1H, d, J = 4.9 Hz), 7.12 (1H, d, J = 2.0 Hz), 7.96 (1H, t, J = 1.5 Hz), 8.31 (2H, d, J = 1.5 Hz), 8.79 (1H, d, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.84, 56.20, 110.07, 100.75, 110.47, 112.61, 123.43, 132.11, 132.86, 139.08, 151.54, 153.34, 154.70, 155.76, 161.58, 162.52; HRMS-ESI (m/z): calcd for $C_{18}H_{14}Br_2NO_4$ $[M+H]^+$: 465.9290, found: 465.9289.

4.1.10.12. 5,7-Dimethoxyquinolin-4-yl 2-iodobenzoate (28). Yield: 82%; mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.68 (3H, s), 3.93 (3H, s), 6.51 (1H, d, J = 2.0 Hz), 7.03 (1H, d, J = 5.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.26 (1H, m), 7.53 (1H, t, J = 7.5 Hz), 8.12 (1H, d, J = 8.0 Hz), 8.26 (1H, dd, J = 7.5, 1.2 Hz), 8.79 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.76, 56.19, 95.62, 99.86, 100.70, 110.82, 112.82, 128.19, 132.46, 132.87, 133.66, 142.20, 151.58, 153.33, 154.88, 155.85, 161.41, 163.89; HRMS-ESI (m/z): calcd for $C_{18}H_{15}INO_4$ $[M+H]^+$: 436.0046, found: 436.0042.

4.1.10.13. 5,7-Dimethoxyquinolin-4-yl 3-iodobenzoate (29). Yield: 85%; mp 176–178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.56 (3H, s), 3.90 (3H, s), 6.46 (1H, d, J = 2.1 Hz), 6.97 (1H, d, J = 4.8 Hz), 7.08 (1H, d, J = 2.1 Hz), 7.26 (1H, m), 7.96 (1H, d, J = 7.9 Hz), 8.16 (1H, d, J = 7.9 Hz), 8.56 (1H, s), 8.76 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.78, 56.08, 94.05, 99.87, 100.69, 110.68, 112.76, 129.58, 130.43, 131.51, 139.22, 142.54, 151.56, 153.35, 154.96, 155.87, 161.45, 163.57; HRMS-ESI (m/z): calcd for $C_{18}H_{15}INO_4$ $[M+H]^+$: 436.0046, found: 436.0042.

4.1.10.14. 5,7-Dimethoxyquinolin-4-yl 4-iodobenzoate (30). Yield: 90%; mp 185–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.56 (3H, s), 3.93 (3H, s), 6.48 (1H, d, J = 2.1 Hz), 6.99 (1H, d, J = 5.0 Hz), 7.10 (1H, d, J = 2.1 Hz), 7.90 (2H, d, J = 8.9 Hz), 7.94 (2H, d, J = 8.9 Hz), 8.78 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.76, 56.02, 99.83, 100.64, 101.77, 110.74, 112.80, 129.09, 131.78, 138.13, 151.53, 153.30, 155.06, 155.86, 161.44, 164.61; HRMS-ESI (m/z): calcd for $C_{18}H_{15}INO_4$ $[M+H]^+$: 436.0046, found: 436.0045.

4.1.10.15. 5,7-Dimethoxyquinolin-4-yl 2-nitrobenzoate (31). Yield: 80%; mp 170–172 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.76 (3H, s), 3.93 (3H, s), 6.53 (1H, d, J = 1.8 Hz), 7.10–7.11 (2H, m), 7.71–7.81 (2H, m), 7.97 (1H, d, J = 7.9 Hz), 8.04 (1H, d, J = 7.2 Hz), 8.81 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.81, 56.30, 100.18, 100.76, 110.71, 112.39, 124.33, 126.40, 130.56, 132.80, 132.90, 151.69, 153.31, 154.23, 155.82, 161.49, 162.99; HRMS-ESI (m/z): calcd for $C_{18}H_{15}N_2O_6$ $[M+H]^+$: 355.0930, found: 355.0925.

4.1.10.16. 5,7-Dimethoxyquinolin-4-yl 3-nitrobenzoate (32). Yield: 90%; mp 210–211 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.58 (3H, s), 3.94 (3H, s), 6.51 (1H, d, J = 2.1 Hz), 7.04 (1H, d, J = 4.9 Hz), 7.12 (1H, d, J = 2.1 Hz), 7.77 (1H, t, J = 8.0 Hz), 8.51–8.57 (2H, m), 8.81 (1H, d, J = 4.9 Hz), 9.09 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.79, 56.13, 100.07, 100.84, 110.34, 112.59, 125.35, 128.13, 130.08, 131.49, 135.98, 148.58, 151.58, 153.42, 154.56, 155.72, 161.51, 162.96; HRMS-ESI (m/z): calcd for $C_{18}H_{15}N_2O_6$ $[M+H]^+$: 355.0930, found: 355.0937.

4.1.10.17. 5,7-Dimethoxyquinolin-4-yl 4-nitrobenzoate (33). Yield: 90%; mp 220–221 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.53 (3H, s), 3.91 (3H, s), 6.68 (1H, d, J = 2.0 Hz), 7.11 (1H, d, J = 2.0 Hz), 7.26 (1H, d, J = 4.7 Hz), 8.38 (2H, d, J = 8.7 Hz), 8.46 (2H, d, J = 8.7 Hz), 8.84 (1H, d, J = 4.7 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 55.64, 56.28, 99.86, 100.63, 109.62, 112.82, 124.18, 131.36, 134.22, 150.64, 151.92, 152.64, 153.92, 155.28, 160.99, 163.06; HRMS-ESI (m/z): calcd for $C_{18}H_{15}N_2O_6$ $[M+H]^+$: 355.0930, found: 355.0932.

4.1.10.18. 5,7-Dimethoxyquinolin-4-yl 3,5-dinitrobenzoate (34). Yield: 81%; mp 251–253 °C; ^{1}H NMR ($CDCl_3$–CF_3COOD, 300 MHz) δ: 3.84 (3H, s), 4.06 (3H, s), 6.87 (1H, s), 7.21 (1H, s), 7.62 (1H, d, J = 6.4 Hz), 8.94 (1H, d, J = 6.4 Hz), 9.43 (3H, s); ^{13}C NMR (CF_3COOD, 75 MHz) δ: 55.80, 56.14, 102.93, 108.67, 112.43, 112.65, 119.93, 123.85, 130.13, 143.86, 148.97, 160.90, 161.47, 162.06; HRMS-ESI (m/z): calcd for $C_{18}H_{14}N_3O_8$ $[M+H]^+$: 400.0781, found: 400.0782.

4.1.10.19. 5,7-Dimethoxyquinolin-4-yl methyl terephthalate (35). Yield: 82%; mp 167–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.53 (3H, s), 3.92 (3H, s), 3.97 (3H, s), 6.48 (1H, d, J = 2.2 Hz), 7.01 (1H, d, J = 5.0 Hz), 7.10 (1H, d, J = 2.2 Hz), 8.20 (2H, d, J = 8.4 Hz), 8.30 (2H, d, J = 8.4 Hz), 8.79 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 52.71, 55.77, 55.98, 99.88, 100.70, 110.68, 112.77, 129.89, 130.41, 133.39, 134.64, 151.58, 153.35, 155.03, 155.84, 161.47, 164.29, 166.32; HRMS-ESI (m/z): calcd for $C_{20}H_{18}NO_6$ $[M+H]^+$: 368.1134, found: 368.1131.

4.1.10.20. 5,7-Dimethoxyquinolin-4-yl 2-fluorobenzoate (36). Yield: 80%; mp 143–145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.62 (3H, s), 3.92 (3H, s), 6.49 (1H, d, J = 2.0 Hz), 7.00 (1H, d, J = 4.8 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.20–7.32 (2H, m), 7.58–7.65 (1H, m), 8.14–8.19 (1H, m), 8.78 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.73, 56.01, 99.83, 100.71, 110.83, 112.83, 117.20, 117.50, 124.26, 132.81, 135.35, 151.60, 153.35, 154.79, 155.89, 160.78, 161.41, 164.25; HRMS-ESI (m/z): calcd for $C_{18}H_{15}FNO_4$ $[M+H]^+$: 328.0985, found: 328.0981.

4.1.10.21. 5,7-Dimethoxyquinolin-4-yl 2-methylbenzoate (37). Yield: 85%; mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.67, (3H, s) 3.61, (3H, s)

3.92 (3H, s), 6.49 (1H, d, J = 2.2 Hz), 6.98 (1H, d, J = 4.8 Hz), 7.10 (1H, d, J = 2.2 Hz), 7.32–7.38 (2H, m), 7.47–7.52 (1H, m), 8.26 (1H, d, J = 7.2 Hz), 8.78 (1H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.84, 55.70, 55.89, 99.67, 100.68, 111.09, 113.04, 126.04, 128.26, 131.75, 132.03, 132.90, 141.71, 151.59, 153.35, 155.28, 155.97, 161.33, 165.30; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1236, found: 324.1230.

4.1.10.22. 5,7-Dimethoxyquinolin-4-yl 2-methoxybenzoate (38). Yield: 83%; mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.66 (3H, s), 3.92 (3H, s), 3.93 (3H, s), 6.48 (1H, d, J = 2.1 Hz), 7.00 (1H, d, J = 4.9 Hz), 7.04–7.11 (3H, m), 7.55–7.60 (1H, m), 8.16 (1H, dd, J = 7.6, 1.8 Hz), 8.76 (1H, d, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.68, 55.95, 56.10, 99.55, 100.57, 111.21, 112.25, 113.17, 118.54, 120.25, 132.88, 134.65, 151.55, 153.30, 155.28, 156.10, 160.39, 161.27, 163.42; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_5$ $[M+H]^+$: 340.1185, found: 340.1189.

4.1.10.23. 5,7-Dimethoxyquinolin-4-yl 4-methoxybenzoate (39). Yield 86%; mp 178–181 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.55 (3H, s), 3.90 (3H, s), 3.91 (3H, s), 6.46 (1H, d, J = 2.1 Hz), 6.98 (1H, d, J = 4.8 Hz), 7.01 (2H, d, J = 8.7 Hz), 7.08 (1H, d, J = 2.1 Hz), 8.18 (2H, d, J = 8.7 Hz), 8.77 (1H, d, J = 4.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 55.49, 55.55, 55.81, 99.48, 100.51, 110.96, 112.92, 113.83, 121.82, 132.41, 151.46, 153.27, 155.30, 155.98, 161.17, 163.83, 164.63; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_5$ $[M+H]^+$: 340.1185, found: 340.1180.

4.1.11. 5,7-Dimethoxyquinolin-4-yl 4-methylbenzenesulfonate (40)

To a solution of **4** (205 mg, 1 mmol) in CH_2Cl_2 (10 mL) at rt was added Et_3N (0.56 mL, 4 mmol) and p-toluene sulfonyl chloride (380 mg, 2 mmol), and the solution was refluxed for 5 h. The reaction was quenched by the addition of water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with diluted hydrochloric acid, saturated $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was recrystallized in MeOH to yield **40**. Yield: 83%; mp 148–149 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.40 (3H, s), 3.76 (3H, s), 3.88 (3H, s), 6.45 (1H, d, J = 2.2 Hz), 6.80 (1H, d, J = 5.0 Hz), 6.99 (1H, d, J = 2.2 Hz), 7.27 (2H, d, J = 8.2 Hz), 7.72 (2H, d, J = 8.2 Hz), 8.63 (1H, d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.79, 55.70, 55.90, 100.06, 100.30, 110.80, 112.06, 128.49, 129.76, 133.48, 145.49, 151.13, 153.20, 153.63, 156.20, 161.62; HRMS-ESI (m/z): calcd for $C_{18}H_{18}NO_5S$ $[M+H]^+$: 360.0906, found: 360.0910.

4.2. Biological assays

4.2.1. Materials

Stock solutions of compounds were prepared with dimethylsulfoxide (DMSO, Sigma) and diluted with RPMI-1640 medium containing 10% fetal bovine serum (FBS). MTT (3-(4,5-dimethylthylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide), Concanavalin A (ConA) was purchased from Sigma (St Louis, Mo). Cyclosporin A (CsA) was obtained from Sandoz Ltd (Basel, Switzerland). [^{3}H]Thymidine (1 mCi/mL) was purchased from Nanjing Medical University. CD25-FITC and CD4-APC antibody were purchased from BD Pharmingen (San Diego, CA).

4.2.2. Animals

Female BALB/c mice (6–8 weeks old, 18–22 g) were supplied by the Laboratory Animal Center of Yangzhou University (Jiangsu, China). They were maintained with free access to pellet food and water in plastic cages at 21 ± 2 °C and kept on a 12-h light–dark cycle. Animal welfare and experimental procedures were carried out strictly in accordance with the 'Guide for the Care and Use of Laboratory Animals' (National Research Council, 1996) and the related ethical regulations of our university. All efforts were made to minimize the animals' suffering and to reduce the number of animals used.

4.2.3. Preparation of spleen cell suspensions

BALB/c mice were sacrificed and their spleens were removed aseptically. A single cell suspension was prepared after cell debris, and clumps were removed. Erythrocytes were depleted with Tris–buffered ammonium chloride (0.155 M NH_4Cl, 16.5 mM Tris, pH 7.2). Lymphocytes were washed three times with RPMI-1640 containing 10% FBS and were resuspended in RPMI-1640 medium supplemented with 10% FBS, penicillin (100 U/mL), and streptomycin (100 U/mL).

4.2.4. MTT assay

Fresh spleen cells were obtained from BALB/c mice (male, 6–8 weeks old). 5×10^5 spleen cells were cultured in triplicate in 96-well flat plates with 200 μL RPMI-1640 media containing 10% FBS, 100 U/mL penicillin, and 100 U/mL streptomycin in a humidified, 37 °C, 5% CO_2-containing incubator for 48 h in the presence or absence of various concentrations of compounds. The cells with media alone were used as control. 20 μL MTT (5 mg/mL) reagent was added 4 h before the end of culture. Then 90 μL of lysis buffer (10% SDS, 50% DMF, pH 7.2) was added to each well for 6 h and the absorbance value at 570 nm was collected by microplate reader. The percentage of cell growth inhibition was determined using the following formula:

$$\text{Cytotoxicity}\ (\%) = (1 - [\text{Compounds}\ (OD_{570}) - \text{Background}\ (OD_{570})] / [\text{Control}\ (OD_{570}) - \text{Background}\ (OD_{570})]) \times 100$$

The compounds were dissolved in dimethylsulfoxide (DMSO) followed by dilution with culture medium to desired concentrations, and DMSO final concentration was 0.1%. DMSO at 0.1% was added into control group and showed no effects on cells.

4.2.5. ConA-induced T cell proliferation assay

Fresh spleen cells were obtained from BALB/c mice (male, 6–8 weeks). 5×10^5 Spleen cells were cultured at the same conditions as those mentioned above. The cultures were unstimulated or stimulated with 5 μg/mL ConA to induce T cell proliferative response. The compounds were added to cultures with desired concentrations to test their bio-activities. The cells stimulated with ConA were used as control. Proliferation was assessed by MTT assay as above. In some experiments, proliferation was assessed in terms of uptake of [^{3}H]thymidine during 8 h of pulsing with 20 kBq [^{3}H]thymidine for each well, and then cells will be harvested onto glass fiber filters by a Basic 96 harvester. The incorporated radioactivity was counted by a liquid scintillation counter.

$$\text{Inhibition rate}\ (\%) = (1 - [^3\text{H}]\ \text{Compound} / [^3\text{H}]\ \text{Control}) \times 100$$

4.2.6. FACS assay of mitogen-induced T cell activation

Fresh spleen cells were obtained from BALB/c mice (male, 6–8 weeks old). 5×10^5 spleen cells were cultured at the same conditions as those mentioned above. The cultures were unstimulated or stimulated with 5 μg/mL ConA to induce T cell activation response. Cells were incubated in the presence or absence of various concentrations of compounds. Twenty four hours later cells were collected and washed with cold PBS twice and stained with CD25-FITC and CD4-APC antibody in 4 °C for 30 min. After washed once with cold PBS, cells were resuspended in 400 μL and applied for FACS assay.

4.2.7. Statistics

All experiments were repeated 3–5 times with the similar outcome. The *p*-values between two experimental groups were tested by two-tailed Student's *t*-test, and *p*-values of 0.05 or less were considered to be statistically significant.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.06.043.

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